Resolving the Gestational Diabetes Diagnosis Conundrum: The Need for a Randomized Controlled Trial of Treatment

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The diagnosis of and criteria for gestational diabetes mellitus (GDM) continue to divide the scientific and medical community, both between and within countries. Many argue for universal adoption of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria and feel that further clinical trials are unjustified and even unethical. However, there are concerns about the large increase in number of women who would be diagnosed with GDM using these criteria and the subsequent impact on health care resources and the individual. This Perspective reviews the origins of the IADPSG consensus and points out some of its less well-known limitations, particularly with respect to identifying women at risk for an adverse pregnancy outcome. It also questions the clinical and cost-effectiveness data often cited to support the IADPSG glycemic thresholds. We present the argument that adoption of diagnostic criteria defining GDM should be based on response to treatment at different diagnostic thresholds of maternal glycemia. This will likely require an international multicenter trial of treatment.

Internationally, there is increasing pressure to adopt the World Health Organization (WHO) 2013 (1) and International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (2) glycemic criteria for gestational diabetes mellitus (GDM). Recent opinion has suggested that it is no longer ethical to carry out randomized controlled trials (RCTs) in this area and has urged universal adoption (3). We disagree with this contention and describe what we consider is the scientific, clinical, and economic argument supporting the need for trials testing different diagnostic glycemic thresholds in this highly contentious field of maternal-fetal medicine.

WHERE DID THE WHO 2013/IADPSG AND CARPENTER/COUSTAN CRITERIA ORIGINATE?

The data used to calculate IADPSG criteria were derived from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study (4). This blinded observational study consisted of 23,316 women with singleton pregnancies from fifteen centers in nine countries tested for glucose tolerance between 24 and 32 weeks' gestation. Venous plasma samples were collected fasting and 1 and 2 h after a 75-g oral glucose tolerance test (GTT) (4). The three neonatal outcome variables with the strongest associations with the fasting, 1-h, and 2-h glucose values (birth weight >90th percentile, cord C-peptide >90th percentile, and percent body fat >90th percentile) were selected for analysis to determine diagnostic thresholds for GDM. A continuous, positive, nearly linear relationship was found between each of the three glucose values and

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prevalence of the three selected outcomes (2). The absence of an inflection point in these relationships made deriving science-based and clinically applicable thresholds to define GDM a substantial challenge. A number of statistical methods for dichotomizing continuous data have been used in analyses of medical data (5,6). Although consensus was acknowledged to be arbitrary (7), this approach for the selection of thresholds was employed by the IADPSG. A plurality selected the glucose values at an adjusted odds ratio of 1.75 (2). Selected threshold glucose values defining GDM were one or more of the following: 5.1 mmol/L fasting, 10.0 mmol/L at 1 h, and 8.5 mmol/L at 2 h following a 75-g glucose load. Exceeding one or more of these three glucose values defined the presence of GDM. For all HAPO participants, including the women whose results were unblinded, this produced a prevalence of GDM of 17.8%.

Because comparisons of the results of application of both the Carpenter/Coustan (CC) (8) and IADPSG (2) test results have been made by several investigators (9–19), it seems relevant to compare and contrast how each set of criteria were derived. The CC criteria (8) are a modification of those derived by O'Sullivan et al. (20), with the former adjusting for method (enzyme vs. reducing substances, respectively) and medium (plasma vs. whole blood, respectively) of the glucose assay used by O'Sullivan et al. Unselected pregnant women ($n = 752$), the majority of whom were either in their second (45%) or third (52%) trimester, were given a 100-g, 3-h GTT. The mean plus 1, 2, and 3 SD for each of the four (fasting, 1-, 2-, and 3-h) GTT results were calculated. Two or more values had to be equaled or exceeded to qualify for the diagnosis of GDM, with the rationale being avoidance of misclassification due to laboratory error or occasional single high peaks resulting from unusually rapid absorption of glucose. These results were then applied to a second cohort of 1,013 women who had been tested for GDM and for nongestational diabetes up to 8 years following their index pregnancy. The values selected to define GDM ($\geq$ mean + 2 SD) were justified by noting that in so doing the resulting population prevalence of GDM approximated the prevalence of nongestational diabetes (1.7%) in a town in eastern Massachusetts (21). Further, a substantially greater proportion of women whose GTT results during pregnancy met the selected thresholds developed nongestational diabetes within 8 years of the index pregnancy (16.1%) than those whose GTT results during pregnancy were normal (0.4%) (20). A similar increased incidence of nongestational diabetes was reported among women found to have IADPSG-defined GDM 11 years after the index pregnancy (22).

Unlike the study by O'Sullivan et al., where results of all participants were considered, in the HAPO study data of women whose GTT results exceeded a fasting glucose of 5.8 mmol/L and/or a 2-h glucose of 11.1 mmol/L were removed from consideration in determining the values defining GDM (2). Had these limits not been set, it seems possible that the glucose values selected by the IADPSG to define GDM may have been higher.

IDENTIFYING WOMEN AT RISK FOR ADVERSE OUTCOMES

The majority of women in the HAPO cohort who had any of the three selected outcomes had GTT results below the IADPSG thresholds. Because the proportion of women who had one or more of the three adverse outcomes and whose GTT results fell below the IADPSG thresholds has not been made available, those relationships may only be approximated. For example, from the HAPO data, 63% of mothers of babies who had a birth weight $\geq$90th percentile had a fasting glucose $<$4.7 mmol/L, 65% had a 1-h glucose $<$8.7 mmol/L, and 66% had a 2-h glucose $<$7.0 mmol/L (4). It is possible that some of these women may have had one or two values equaling or exceeding the IADPSG thresholds, but it is equally clear that these glucose values are well below the IADPSG criteria. Thus, it may be reasonable to infer that a large proportion of the women at risk for this adverse outcome would not be identified as having GDM.

Of possible greater concern is the finding that among those identified as having untreated GDM by IADPSG criteria, the majority did not have any of the three adverse outcomes. For example, in the highest categories of fasting, 1-h, and 2-h glucose values in the HAPO study (respectively $>$5.6 mmol/L, 11.8 mmol/L, and 9.9 mmol/L), more than 74% of women had a baby whose birth weight was $<$90th percentile (4). Identifying women who are not at risk for adverse outcome as having GDM is not without consequence. The economic concerns are discussed below, but there are also personal and psychological consequences of informing a woman that she has GDM. Time away from home and work imposed by increased surveillance, purchase of alternative foods, and the requirement for glucose self-monitoring pose burdens beyond those of normal pregnancy (23,24). Conflicts with cultural practices (e.g., alternative eating regimens, lack of incorporation of traditional foods) are sources of stress (23,25), as are concerns that the woman's "illness" may adversely affect both her and her baby's health (24). Using a standard quantitative survey of well-being (SF-36), one study reported that women who had GDM scored significantly lower than healthy control subjects on the general health perception subscale and that those differences persisted following delivery (26). Imposing a diagnosis of GDM on women who may not benefit from treatment and whose quality of life may be impaired by having been given that diagnosis is a significant concern.

THE NEED FOR UNIVERSAL CRITERIA DEFINING GDM

Worldwide, the adoption of the IADPSG criteria, or lack thereof, appears to reflect the variety of opinions of their clinical value and cost. The International Federation of Gynecology and Obstetrics (27), the Australasian Diabetes in Pregnancy Society (28), and the WHO (1) have endorsed the IADPSG testing procedure and definition of GDM. While acknowledging that either the CC or IADPSG strategies may be used to diagnose GDM, the American Diabetes Association recommends the latter (29). The American College of Obstetricians and Gynecologists (30), the U.K. National Institute for Health and Care Excellence (NICE) (31), the Diabetes in Pregnancy Study Group of India (32), and the Canadian Diabetes Association (33) have each adopted diagnostic tests which differ in the use of a preliminary screening test, glucose load, number of glucose values that must be equaled or exceeded, and glycemic thresholds.

Table 1—Changes in GDM prevalence and outcomes comparing older to IADPSG criteria. Except for reference 52, all were "before and after" studies

		Total deliveries				Change with IADPSG				
Ref. no.	Country	*n* before change	*n* after change	Previous criteria	% GDM previous	% GDM IADPSG	C/S	HDP	Fetal overgrowth	NN Hypo
11	Taiwan	3,056	3,641	CC*	4.6	12.4	NS	NS	↓	NR
12	Switzerland	NR	NR	CC*	5	11	NS	NS	NS	↓
13	U.S.	471	332	CC*	5.5	16	NS	NS	NS	NS
18	Spain	1,750	1,526	CC*	10.6	35.5	↓	↓	↓	NR
43	Slovenia	135,786	140,524	CC*	2.6	9.7	↑	↓	↓	↑
44	Japan	3,912	4,772	†	2.9	13	NS	NR	NS	↓
45	Belgium	3,496	2,553	‡	3.4	16.3	NS	NS	NS	NS
46	Australia	3,553	6,724	ADIPS§	3.4	3.5	NS	NR	↓	NR
47	Croatia	2,359	3,157	WHO‖	2.2	12	NS	NR	NS	NR
48	Switzerland	647	720	‡	3.3	11.8	NS	NS	NS	NS
49	Australia	7,010	7,488	ADIPS¶	5.9	10.3	NS	NS	NS	NS
50	Taiwan	888	952	CC*	2.6	13.4	NS	NS	NS	NS
51	Australia	62,517	61,600	ADIPS¶	8.7	11.9	NS	↑	NS	↑
52#	Malaysia	261	259	WHO‖	37.9	38.6	NS	NS	NS	NS

C/S, cesarean section; HDP, hypertensive disorder of pregnancy; NN Hypo, neonatal hypoglycemia; NS, not significant; NR, not reported. *Carpenter/Coustan (8). †75-g GTT, ≥2 exceeded: fasting, 100 mg/dL (5.6 mmol/L); 1-h, 180 mg/dL (10 mmol/L); 2-h, 150 mg/dL (8.3 mmol/L). ‡75-g GTT, ≥2 exceeded: fasting, 95 mg/dL (5.3 mmol/L); 1-h, 180 mg/dL (10 mmol/L); 2-h, 155 mg/dL (8.6 mmol/L). §Australasian Diabetes in Pregnancy Society 1991 criteria (74). ‖World Health Organization 1998 (75). ¶Australasian Diabetes in Pregnancy Society 1991 (74) and 1998 (68) criteria. #Randomized controlled trial; WHO 2013 (1).

An argument for universal rather than selective risk factor–based screening, particularly in low- and middle-resource countries that have a high prevalence of diabetes, has been made (34). Likewise, because of the poor sensitivity, specificity (35), and reproducibility (36) of post-glucose screening tests, along with patient inconvenience and noncompliance with return for the definitive diagnostic test (37), the argument for a one- versus two-step procedure for diagnosis of GDM has merit (17,38). However, the cost effectiveness of universal screening has been challenged in high-resource settings where risk factors identify those women who are more likely to have GDM. In the HAPO study, the prevalence of IADPSG-defined GDM varied substantially from one center to the next, with the highest (25.5%) at a U.S. center and the lowest (9.3%) at an Israeli center (39). Particularly in populations where IADPSG-defined elevated GTT glucose values are not associated with increased risk of adverse outcomes (40–42), universal criteria defining GDM may both be wasteful and contribute to unnecessary patient anxiety. For purposes of data comparison, universal criteria may be useful, but for patient care, there may be little benefit. Individual populations may require treatment at different glycemic thresholds in order to achieve comparable outcomes.

THE NEED FOR AN RCT OF TREATMENT

There have been several studies comparing IADPSG criteria to historical controls (11,12,14,18,43–51), as well as one RCT (52), with inconsistent results, perhaps due to the utilization of a before-and-after analysis (53). The results are summarized in Table 1. The evidence from these studies suggests that despite an increase in prevalence of GDM using the IADPSG screening protocol, treatment does not seem to substantially reduce adverse outcomes in comparison with the epochs when women were diagnosed with criteria that gave a much lower population prevalence.

The fasting, 1-h, and 2-h thresholds for the IADPSG and CC criteria (fasting ≥5.1 mmol/L and ≥5.3 mmol/L; 1-h ≥10.0 mmol/L for both; and 2-h ≥8.5 mmol/L and ≥8.6 mmol/L, respectively) (2,8) are similar. In an analysis of data from five of the HAPO centers ($n = 6,159$) at which all subjects were given a 75-g 2-h GTT, 14.3% of subjects were identified as having GDM by a single elevated IADPSG value, while 4.2% of the same cohort had GDM using two or more of the CC thresholds. Despite the similarity in glycemic thresholds for each individual time point, the fasting, 1-h, and 2-h glucose concentrations of those identified as having GDM by the CC criteria of two or more abnormal values were significantly greater than the results of those women identified as having IADPSG GDM with a single elevated value. Of note is that the adjusted odds ratios for the three adverse outcomes used by the IADPSG were numerically greater for the CC group than for the IADPSG group (54).

Making global inferences about the quantitative relationships between adverse outcomes and GDM when the latter is defined by different criteria is concerning. The argument has been advanced that no study of the results of treatment of GDM identified by IADPSG criteria is warranted and may, indeed, be unethical because two prior RCTs showed benefit of treatment of GDM (55,56). However, each of these studies employed different glucose loads, different number(s) of elevated GTT results, and different glycemic thresholds from IADPSG to define GDM, as well as different glycemic thresholds for initiation of insulin treatment. Neither study used IADPSG criteria to identify women with GDM. Thus, while both studies demonstrated a benefit of treatment of GDM, it is by no means certain that women

Table 2—Estimated differences in maternal and neonatal outcomes for the U.K. and Australia HAPO data set using different glycemic thresholds for a diagnosis of GDM*

Diagnostic threshold (mmol/L)	Number diagnosed	Shoulder dystocia	Serious perinatal complications	Cesarean section	NICU admission	Neonatal jaundice	Preeclampsia	Induction of labor
None	0	73	100	1,224	533	345	201	621
FPG ≥5.6, 2-h ≥7.8 (NICE)	837	64	87	1,199	510	335	175	1,662
IADPSG or 2.0, FPG ≥5.3, 2-h ≥9.0	569	66	91	1,207	518	338	182	1,649
IADPSG or 1.75, (WHO 2013) FPG ≥5.1, 1-h ≥10.0, 2-h ≥8.5	1,165	62	85	1,190	505	331	168	1,676
IADPSG or 1.50, FPG ≥5.0, 2-h ≥7.9	1,399	60	82	1,184	499	329	163	1,676
Close to ADIPS, FPG ≥5.5, 2-h ≥8.5	543	66	91	1,207	518	338	182	1,647

*Reproduced from: Royal College of Obstetricians and Gynecologists, NICE Guideline 3 'Diabetes in pregnancy (Table 117 of page 587)', London, RCOG, February 2015, with the permission of the Royal College of Obstetricians and Gynecologists (31).

diagnosed using IADPSG criteria would show the same results.

We agree with Hod et al. that "questions both of individual clinical and broader public health risks and benefits, opportunity costs, and health economics must be considered when a decision is being made about diagnostic processes and cut-off values" (3). However, the cited studies do not address the cost-effectiveness of adopting the IADPSG criteria and are more concerned with comparing a one-step versus a two-step diagnostic approach (57–61).

It has been argued that changing to IADPSG criteria would have significant cost savings by reducing cesarean rates and neonatal intensive care unit admissions despite the increased treatment costs from a threefold increase in GDM (18). This was based upon a before-and-after study from a single center in Spain. The authors reported a 24% reduction in cesarean sections across the whole population of pregnant women following the change to IADPSG (18), but the new criteria could only explain a reduction in cesarean rates in the minority of patients who would be newly diagnosed and treated with IADPSG criteria, and therefore the percentage reduction in cesarean rates in this subgroup would have to be much greater than 24% in order to explain such a large reduction across the entire population. This far exceeds the reported impact of early GDM treatment from RCTs and suggests that other changes in clinical practice are more likely to have had an impact.

Two studies from the U.K. (62,63) have specifically addressed the cost effectiveness of using different diagnostic thresholds for GDM, and neither found IADPSG criteria to be cost-effective. One (62), based upon data from the U.K. and Australian HAPO centers, together with the Atlantic Diabetes in Pregnancy (DIP) study (63), found a fasting blood glucose of ≥5.6 mmol/L and/or 2-h of ≥7.8 mmol/L (the NICE criteria) to be more cost-effective than IADPSG for women with preexisting risk factors for GDM. Universal population screening was not found to be cost-effective. Neither of these studies considered potential long-term benefits of reduction in diagnosis of type 2 diabetes in the mother and/or offspring as they could find no conclusive data demonstrating a positive benefit. Published data on these outcomes are inconclusive (64,65) and therefore would not have a significant impact in cost-effectiveness modeling. As they stand, the IADPSG thresholds do not appear to meet cost-effectiveness criteria, at least in the U.K. setting, and this consideration is even more important for countries with limited health care resources.

We suggest that an RCT to assess the effects of treating or not treating women with GDM should be conducted. While the design of such a trial is beyond the scope of this article, a few considerations bear mention. For reasons previously stated as well as diurnal variation in response to a glucose challenge (66), a preliminary glucose screening test should be dispensed with. The glucose load, gestational age for testing, and the number of values to be equaled or exceeded need to be standardized. To determine the need for lower glucose concentrations to define GDM, the thresholds for intervention should be set at glucose concentrations at or above those used in most of the participating centers. For determination of the applicability of results to different populations, the participants should ideally be multi-institutional and multinational. Most European, North American, and Australasian centers have diverse populations with a wide range of ethnic backgrounds, which would help meet this requirement. Treatment, both dietary and pharmaceutical, could be left to local teams with proposed target ranges and suggested treatment regimens applicable to local practice and availability. The study would need to be double blinded as per previous studies (55,56). There is reasonable agreement about the outcomes of relevance, and a recent consensus publication (67) has listed those of most importance. We feel that a critical outcome is large for gestational age with its potential sequelae of increased risk of traumatic delivery and caesarean birth, which are proxy outcomes typically used in previous studies. Other key outcomes for consideration would be those with both individual and health economic implications, such as differences in maternal hypertensive disorders and intensive care requirement for the neonate. While this latter outcome is perhaps more relevant for

specialist centers, the high cost of this provision has important health economic implications. Additionally, long-term follow-up of study participants might provide information about potential benefit of diagnosing and treating GDM vis-à-vis prevention of subsequent type 2 diabetes.

An indication of the numbers that would be required for such a study are available from the NICE 2015 guideline analysis of 6,221 U.K. and Australian women who took part in the HAPO study (31). Outcomes for assessment in this analysis were agreed in advance by a multidisciplinary group, but they did not include large for gestational age alone as it was felt that the consequent complications for mother and neonate were of more importance. The analysis of these women, with various degrees of untreated glucose intolerance, used the effects of treatment as determined in the two previous randomized treatment trials. Table 2 shows the estimated effects of treatment at various thresholds, and these data should assist in estimating the numbers required for an RCT using the selected outcomes of interest. An RCT comparing the results of treatment of pregnant women whose GDM is defined in the "lower" group by IADPSG criteria and in the "higher" group by current local (Australasian [68]) criteria is currently in progress (69). This study may help clarify at which maternal glycemic thresholds treatment makes a difference in decreasing neonatal morbidity without increasing maternal morbidity. However, the global generalizability of the results of this trial will be limited by there being only two participating institutions, both in the same country.

CONCLUSIONS

We concur that binary criteria defining GDM have both scientific and clinical merit, and for the foregoing reasons we also feel that a one-step diagnostic procedure is preferable and justified. For most common adverse pregnancy outcomes, a change to the IADPSG criteria from previous diagnostic criteria has not made a major difference other than increasing the prevalence of GDM (Table 1). However, worldwide variation in the prevalence of IADPSG-defined GDM in the HAPO study (39) and the differences in posttreatment outcomes in studies from different parts of the world (Table 1) suggest that different populations may benefit from treatment at different glycemic thresholds. Establishing those thresholds will require a multicenter, multinational RCT of treatment. Both the WHO 2013 guidance (1) and the National Institutes of Health Consensus Panel (70) recommended the undertaking of cost-benefit, cost-effectiveness, and cost-utility analyses to more fully understand the resource implications of changing the diagnostic thresholds for GDM. The output of a treatment trial using the IADPSG criteria as a basis for patient selection will likely address these needs and may also support a resetting of diagnostic as well as therapeutic thresholds to better assure improved patient outcomes.

Until the results of a large, multinstitutional study are known, it seems prudent to propose a set of diagnostic criteria that are safe, have potential patient benefit, and are cost-effective within the constraints of the availability of resources in an individual country setting. Treatment with a change in diet has been shown to decrease the incidence of GDM (71–73). Given this observation, we propose, first, that *all* pregnant women at their first prenatal visit be given dietary advice to try to prevent GDM. Second, we propose no changes in gestational age at testing or number of values to be equaled or exceeded to identify GDM, but we suggest that each health care service adopt diagnostic criteria based upon local available data on clinical and cost-effectiveness, practicality of test, and local resources. While we recognize that this has the disadvantage of using different diagnostic criteria in different regions, we feel that this is the most practical current recommendation pending the results of a suitably powered RCT. We respectfully submit these suggestions in the hope that they will provoke meaningful dialog and, ultimately, benefit the pregnant women for whom we care.

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